New treatment mechanisms for schizophrenia

January 8 2008

The field of schizophrenia research has come alive with many exciting new potential approaches to treatment. From the introduction of chlorpromazine to the current day, all treatments approved by the U.S. Food and Drug Administration have had, at their core, a single treatment mechanism, the blockade of the dopamine D2 receptor.

The introduction of clozapine in the 1980's suggested a potential that other brain targets might complement the blockade of dopamine D2 receptors to treat symptoms that failed to respond to the "typical" antipsychotics. We are now entering an age where new treatments are being rationally developed within the context of translational neuroscience, i.e., the steps whereby basic molecular neuroscience leads to fundamental new mechanisms that can be tested in animal and human laboratory-based research that, in turn, leads to tests of new medications in our clinics. The January 1st issue of *Biological Psychiatry* includes encouraging new research related to three new treatment approaches.

In the first study, Olszewski and colleagues tested a novel drug that inhibits the breakdown of the transmitter N-acetylaspartylglutamate (NAAG), which activates a receptor that reduces schizophrenia-like behaviors in some animal models. Their findings indicate that this drug is effective in an animal model of schizophrenia. Joseph H. Neale, Ph.D., lead author on this project, comments, "While treating patients with receptor agonists can be highly effective therapy, drugs that increase the action of the transmitter that activates the same receptor have traditionally been very effective with fewer side effects than

chronic agonist treatment." He adds, "These data support the conclusion that NAAG peptidase inhibitors represent a breakthrough in the discovery of a completely novel means of adjunct therapy for schizophrenia that is analogous to the use of SSRIs [selective serotonin reuptake inhibitors] for the treatment of depression."

In the second article, Hashimoto and colleagues demonstrated that repeated administration of the N-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) decreased the density of α7 nicotinic receptors (α7 nAChRs) in the mouse brain, and that the novel α7 nAChR agonist SSR180711 could ameliorate PCP-induced cognitive deficits in mice. According to Kenji Hashimoto, Ph.D., head author for this study, the impetus for this study came from the fact that "accumulating evidence suggests that α7 nicotinic receptors, a subtype of nicotinic receptors, are a most attractive target for novel therapeutic drugs of neuropsychiatric diseases including schizophrenia and Alzheimer's disease. Behavioral abnormalities in animals after repeated administration of the NMDA receptor antagonist phencyclidine (PCP) have been used an animal model of schizophrenia." These findings suggest that α7 nAChR agonists including SSR180711 could be potential therapeutic drugs for cognitive deficits in schizophrenic patients.

In the third investigation, Semenova and colleagues show that a recently discovered brain receptor for serotonin (5-HT7) might be of importance for understanding certain aspects of schizophrenia. Their study focused on sensory input processing, which is often impaired in schizophrenia, and finds that blockade of this particular serotonin receptor in mice alleviates this impairment. Peter B. Hedlund, M.D., Ph.D., senior author, notes: "Certain pharmaceuticals used to treat schizophrenia interact with this receptor. Our results indicate that especially so-called atypical antipsychotics may promiscuously exert some of their beneficial effects through the 5-HT7 receptor. Further exploration of this receptor as a treatment target may lead to more specific and better medications for

disorders such as schizophrenia."

John H. Krystal, M.D., Editor of Biological Psychiatry and affiliated with both Yale University School of Medicine and the VA Connecticut Healthcare System, comments, "It is very clear that very few tested medications actually become new treatments. However, the embedding of clinical research within the framework of translational neuroscience increases the likelihood that one or another of these mechanisms might someday emerge as a treatment for schizophrenia." Dr. Krystal concludes, "Since we have so few mechanistically distinct approaches for the pharmacotherapy of schizophrenia, the possibility of the emergence of new treatment mechanisms is certainly a source of hope."

Source: Elsevier